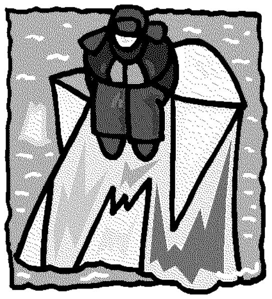
Basic Concepts for Mixtures Risk Assessment

Why Are Mixtures an Issue? Every day we are exposed to different combinations of chemicals in our homes, at work, in food, and in the environment (air, water, and soil). These mixtures can be composed of tens, hundreds, or even thousands of different chemicals. To further complicate matters, each chemical could have several toxic effects, ranging from cancer to different kinds of noncancer or *systemic* effects. A question



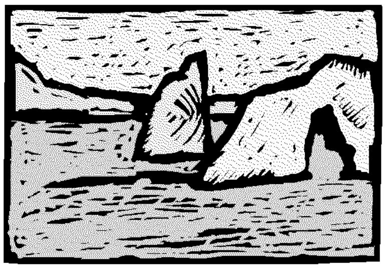
commonly asked is: How could the combined chemicals affect my health? Risk assessment has historically looked at effects from single chemicals then simply added the risks together, so in a way this is looking at the "tip of the iceberg" for chemical mixtures. To better evaluate the many cumulative exposures and effects that could be possible, approaches are being developed to assess risks more comprehensively. The U.S. Environmental Protection Agency (EPA) first published risk assessment guidelines for mixtures in 1986, with an update in 2000. The Agency formally defined a cumulative risk policy and offered planning and scoping guidance in 1997, and a cumulative risk assessment framework was published in 2003 following extensive input from many people. Three types of cumulative risk "icebergs" are worth noting: interactions, exposures, and effects.

What Are Toxic Interactions? We might understand the toxic effects of certain chemicals in the mixtures to which we are exposed, but we simply don't have this information for all possible mixtures. Where appropriate data exist for the mixture itself, such as diesel exhaust or cigarette smoke, it is evaluated as a whole mixture. Where such data are not available, information about the individual chemicals in the mixture is used, considering their proportions and relative toxicities. We usually assume each chemical would cause the same harm regardless of whether it was in a mixture or by itself. Thus, *dose addition* is our basic assumption, where the toxicity of a mixture is predicted by adding the toxicities caused by the doses of its individual chemicals, as adjusted to account for their relative toxicities. For example, if a mixture has two chemicals in equal amounts and the first is twice as toxic as the second, the toxicity of the mixture would be the same as adding three doses of the first. The special case where the chemicals are toxicologically independent (i.e., cause harm in different ways) is described by *response addition*. Here, the combined toxic response is the same as if the responses caused by the individual chemicals were added. For instance, tranquilizers and alcohol both depress the central nervous system but by different means. If a person is exposed to both, the effect on the central nervous system is the same as the sum of the effects caused by each separately.

In fact, the toxicity of a mixture might be lower or higher than predicted from the known effects of each chemical acting alone. The influence one chemical has on the toxic effect of another is called a *toxic interaction*. The EPA mixtures guidance identifies toxic interaction as being something other than our default assumption of simple addition. Four types of interactions have been defined, relative to dose addition (see box). A *synergistic* interaction can be illustrated by alcohol and the solvent carbon tetrachloride, each of which harms the liver. Exposure to both damages the liver much more than predicted by simple dose addition. An *antagonistic* interaction can be illustrated by arsenic and lead. Exposure to both causes less harm to the kidney and blood than predicted by dose addition. *Potentiation* can be illustrated by carbon tetrachloride and isopropanol, which is rubbing alcohol (also found in perfume) and is not considered a liver toxin. Inside the body, isopropanol interacts with carbon tetrachloride and causes it to damage the liver more than it would have alone. *Inhibition* is the basis of some antidotes, where you take a dose of a chemical that does not harm you to reduce the harmful effect of another. When risks are estimated by assuming only dose or response addition without considering toxic interactions, perhaps only the tip of the iceberg is being addressed.

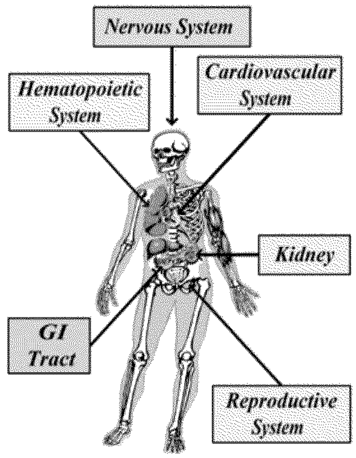
Interaction	Definition
Synergism	The combined effect of two or more chemicals is > predicted by dose addition
Antagonism	The combined effect of two or more chemicals is < predicted by dose addition
Potentiation	Exposure to one chemical that is not toxic itself increases the toxicity of second chemical when exposed to both
Inhibition	Exposure to one chemical at a nontoxic dose decreases the toxic effect of another

What Are Mixture Exposures? Some mixtures are manufactured before they are released to the environment (like a specific pesticide formulation), while others are formed during combustion (such as in our car engines) or by other chemical transformations. Chemical interactions in the environment can alter the composition and behavior of a mixture over time. We are exposed to mixtures everywhere. For example, when we breathe outside



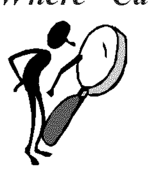
we can be taking in a mixture of all the air emissions from point sources (such as chimneys and smokestacks) and mobile sources (such as cars, buses, and planes) in the area. This led many federal programs to look more closely at cumulative exposures at the community scale, beginning in the 1990s, by studying releases alone or by combining modeling with emissions measurements. For example, a regional air impact modeling initiative (RAIMI) launched by EPA in 1999 considers risks at the neighborhood level from exposure to multiple air contaminants from multiple sources and pathways; the initial RAIMI study was completed for an area in Jefferson County, Texas. This type of integrated assessment has been pursued under several national programs. These include the Cumulative Exposure Project (CEP), the National-Scale Air Toxics Assessment (NATA), the Residual Risk Report to Congress, and the Integrated Urban Air Toxics Strategy. These types of assessments look at combined doses from many sources rather than only considering the chemicals from a single location. A fuller look at this second exposure "iceberg" considers lifestyle-related exposures, such as to household pesticides and cigarettes.

What Are Mixture Effects? In addition to considering the combination of chemicals in environmental mixtures and the many ways we can be exposed to them, we also have to realize that each chemical in a mixture could cause multiple health effects. Under the classic risk assessment approach, the *critical* or *primary effect* is generally the most sensitive effect (that first seen as the dose is increased above the level where no adverse effects are observed), and it is often determined from animal studies; this generally serves as the basis for the toxicity value we use to estimate human health risks. However, virtually all chemicals can also have *secondary effects*, which do not occur until we are exposed to larger amounts. Information about primary effects and some secondary effects is contained in EPA's Integrated Risk Information System (IRIS) and in the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological and interaction profiles, each of which are available on-line. As science progresses, we will continue to improve our ability to evaluate the role of secondary effects. This is important because in theory, risks calculated based only on critical effects might not be considered a problem if the chemicals in a mixture each impact different organs (e.g., liver) or systems (e.g., nervous system) at tolerable levels. However, the evaluation of possible adverse health effects should extend beyond the chemicals' primary targets to also consider their cumulative impact on other organs or systems that could be harmed as exposures increase. This requires an extensive toxicity evaluation. In a sense, assessing only the primary effects might miss important cumulative secondary effects – a third "iceberg" to keep in mind.



Where Is the Science Taking Us? In the past, risk assessments have typically evaluated risks from distinct chemicals, operations, processes, waste streams, or contaminated media. As assessment methods keep pace with emerging scientific knowledge, EPA and others will continue to further evaluate contributions from (1) other pollutants and processes beyond those at the facility being assessed, (2) many sources of a single pollutant in a given community, and (3) the combination of sources, chemicals, and exposures that affect a given community. Interactions among chemicals and the cumulative result of secondary effects are being considered as part of these enhanced assessments. Additional research will better illuminate the often "hidden" components of cumulative health risk from environmental exposures.

Where Can I Find More Information? Key sources include: the EPA mixtures guidance



(http://www.epa.gov/ncea/raf/pdfs/chem_mix/chem_mix_08_2001.pdf), cumulative risk framework (http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=54944.), IRIS (http://www.epa.gov/iris), and cumulative risk resource document (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190187), as well as ATSDR interaction profiles (http://www.atsdr.cdc.gov/interactionprofiles/index.asp).